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Baron & Warren 18 South End Kensington  
London W8 5BU(GB)(54) **Pharmaceutical composition in sustained release unit dose form and process for its preparation.**

(57) A pharmaceutical composition of a medicament, such as a 5-(pyridinyl)-2(1H) pyridone, in sustained release unit dosage form for oral administration. The composition is in the form of beads within a capsule of gelatin or the like. Each bead comprises an inert particulate core having adhered thereto a coating of particles of the medicament. This coating is in turn surrounded by a sustaining coating of three different polymers with different solubility profiles to allow a sustained release of the medicament both in the low pH environment of the stomach and at a higher pH values prevailing in the intestine.

"PHARMACEUTICAL COMPOSITION IN SUSTAINED RELEASE  
UNIT DOSE FORM AND PROCESS FOR ITS PREPARATION"

1        This invention relates to a sustained release  
form of a medicament for administration by the oral  
route.

         The use of enteric coatings on medicaments in  
5        order that the medicaments shall pass through a patient's  
stomach unchanged and thus ensure that the active  
ingredient or ingredients are released in the patient's  
small intestine where the pH is normally between  
5.5 and 7.5 is now an established method of treatment.  
10       This prevents irritation of the gastrointestinal  
tract and is often convenient as it may make it  
unnecessary for a patient to take a dose of medicament  
more often than two or three times a day to maintain  
effective blood levels of medicament. A substantial  
15       number of synthetic polymeric materials have been  
proposed for use in such formulations and the nature  
of the coatings used in the formulations have varied  
considerably depending upon the results sought.  
         Thus the synthetic polymeric materials used have  
20       included polymers of vinyl monomers such as vinyl  
pyrrolidone and vinyl acetate phthalate and the semi-  
synthetic derivatives of celluloses such as cellulose  
ethers and carboxycelluloses, e.g. cellulose acetate  
25       phthalate and hydroxypropylmethyl cellulose phthalate.

         In some cases partial solution of a medicament  
in the patient's stomach is required especially if  
gradual solution in both the stomach and the small  
intestine is the desirable course to aim at. This  
30       presents problems because of the differences in the  
pH values prevailing in the stomach and the intestine,  
and in the differences in the chemical and physical

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1 properties of particular medicaments when submitted  
to these differing pH conditions. In general the  
differences are most difficult to overcome with medic-  
aments containing one or more amino groups in the  
5 molecule. Individual solutions have to be found  
to the particular problems posed by each system.

In two or three cases in which the medicament  
is only soluble at pH values between 1 and 4 solution  
can take place naturally in the stomach but does  
10 not occur at all in the small intestine. To overcome  
this difficulty it has been proposed to include a  
readily soluble pharmacologically acceptable acid  
in the inner or core portion of each unit of medicament:  
the amount of this acid may be two or more molecules  
15 for each molecule of medicament and it enables sufficiently  
acid conditions to be set up locally in the small  
intestine for the medicament to dissolve and be absorbed  
through the walls of the intestine. The core is  
surrounded by a semipermeable coating containing  
20 a mixture of film-forming materials one of which  
is soluble and the other of which is insoluble in  
the gastric juices (see US-A-4 361 546, 4 367 217  
and 4 438 091). It will be appreciated that in this  
way a gradual release of medicament can be brought  
25 about and consequentially there is gradual absorption  
through the walls of the stomach and the small intestine.  
However it is limited to the particular solubility  
characteristics indicated for the medicament.

A different problem arises when a medicament  
30 has a high solubility in the low pH gastric

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1   juices and a very much lower solubility in the  
higher pH intestinal juices, which lower  
solubility may nevertheless  
be sufficient for a sustained release formulation.

5   We have now encountered a group of medicaments in  
which such solubility characteristics have been found  
to exist and for which a sustained release formulation  
is required.

10       IN GB-A-2 065 642 there are described a number  
of 5-(pyridinyl)-2(1H) pyridones which are reported  
to be useful as cardiogenic agents. Certain of these  
compounds have been found to show promise for use  
in vivo and to be potential materials for use with  
human patients but they have one important drawback  
15   viz that they are very readily eliminated from the  
human system as demonstrated by the plasma profiles  
obtained after administration to human patients.  
These compounds have been found to have much greater  
solubility in the gastric juices at pH 1.5 than they  
20   have at pH 4.5. In one instance the solubility is  
substantially fifty times greater at pH 1.5 than  
it is at pH 5 to 8.

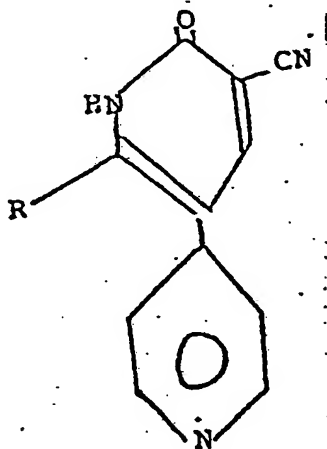
It is accordingly an object of this invention  
to provide a sustained release form of the above  
25   mentioned medicaments and others that are orally  
administered and have a high solubility in gastric  
juices but are very readily eliminated from the human  
system, which form will overcome this drawback.

Accordingly the invention consists in a pharma-  
30   ceutical composition of a medicament in sustained  
release unit dosage form for oral administration,  
comprising a plurality of beads within a closed container  
of a gastric juice-soluble material, characterised  
in that each said bead has an inert particulate core

1 having adhered thereto a coating of particles of said  
medicament, said coating of medicament being surrounded  
by a sustaining coating comprising at least three admixed  
5 polymers, a first said polymer being soluble in gastric  
juices at all pH values encountered in the gastrointes-  
tinal tract, a second said polymer being substantially  
insoluble in gastric juices at pH values below 3 but sol-  
uble therein at pH values of 5 and above and the third  
10 said polymer being insoluble in the contents of the  
gastrointestinal tract at all pH values normally  
encountered therein, and the three polymers being  
present in such proportions as to permit a substant-  
ially uniform release of the medicament during passage  
of the beads through the stomach and gastrointestinal tract..

15 It is preferred that the weight of the polymer  
which is insoluble in the contents of the gastrointestinal  
tract is greater than the sum of the weights of the  
other two polymers present in the sustaining coating.  
A convenient ratio of the weight of the insoluble  
20 polymer to the combined weights of the other two  
polymers present in the sustaining layer has been  
found to be from 3 : 2 to 2 : 1.

The invention has been found to have a particular  
application to the formulation in unit dosage form  
25 for administration by the oral route of pyridyl-(1H)  
pyridones having the general formula



(I)

1 in which R is an alkyl group having 1 to 4 carbon  
atoms. With such materials it has been found that  
upon administration by the oral route the concen-  
tration of the medicament in the plasma rises very  
5 rapidly during the first hour and then falls by approx-  
imately two-thirds of the maximum reached during the  
second hour. Subsequently it falls at a somewhat  
diminishing rate during the third and subsequent hours.  
If a single dose is to be sufficient to maintain effec-  
10 tive blood levels in a patient for a substantial number  
of hours e.g. 4 or 8 hours a system needs to be  
devised in which only a portion of the dosage is made  
available for absorption into the blood at any one time.  
Continual release of the medicament will maintain effective  
15 blood levels until the next dose of medication is taken. The  
rate of dissolution (and therefore availability) has  
been found to be determined by the pH of the  
particular part of the gastrointestinal tract.

It has been found that in the case of the  
20 pyridyl-pyridones the rate of dissolution is greatest  
in the range of lowest pH value which is in the  
stomach and the rate of dissolution decreases as the pH  
rises along the passage of the upper gastrointestinal  
tract.

25 Consequently the polymers used and the proportions  
of these in the sustaining layer will determine the  
release characteristics of the medicament from the  
dosage form.

We prefer to use nonpareils as the inert substrate  
30 material of the beads that we prepare.

The substrate is then coated with particles

1 of the medicament in solid form. It may be necessary  
to convert a medicament to a derivative such as a  
salt in order to obtain it in solid form. Medicaments  
available in solid form may need to be ground in  
5 order to obtain particles sufficiently small to be  
conveniently adhered to the particles of core material.  
The latter are conveniently of a size which will  
pass a 25 US standard mesh and be retained on a 30 US  
standard mesh. To adhere the particles of solid  
10 medicament to the inert substrate we prefer to use  
a water soluble pharmacologically acceptable adhesive  
such as a suitable grade of hydroxypropylmethylcellulose.  
The hydroxypropylmethylcellulose used may be that known  
as "Pharmacoat 606", a 6-centipoise grade of hydroxy-  
15 propylmethylcellulose. A thorough dispersion of the  
solid medicament in Pharmacoat 606 solution is then  
prepared and used to coat the nonpareils or other  
particulate inert substrate material in a coating  
column and dry the coated material at a raised temp-  
20 erature, e.g. 60°C.

The sustaining coating essentially contains  
three polymers each of which behaves differently in  
the gastrointestinal tract. All three polymers may  
be cellulose derivatives and each of the polymers  
25 may be a mixture. However, whether each be a single  
individual or a mixture it must conform to certain  
solubility requirements in relation to the gastro-  
intestinal tract.

The first polymer should be soluble in the gastric  
30 juices at all pH values encountered in the stomach and  
the intestine. In the case of the pyridyl pyridones  
this includes the pH range over which these substances  
exhibit their maximum solubility in the gastric juices:

- 1 when this is the case the preferred polymer is hydroxy-  
propylmethylcellulose. Other polymers which may be  
used for this purpose include polyvinylpyrrolidone  
and sodium carboxymethylcellulose. When it is  
5 essential to reduce the rate of dissolution of the  
medicament at pH values of the order of 1.5 the  
proportion of this polymer in the mixture of polymers  
should be kept low e.g. 15% - 20% or less by weight  
of the whole mixture of polymers.
- 10 The second polymer used is one which is sub-  
stantially insoluble in gastric juices at pH values  
below 3 but soluble therein at pH values of 5 and  
above. The use of such a polymer ensures that while  
this part of the coating remains substantially intact  
15 at the pH values normally encountered in the stomach,  
typically 1.5 - 2.0, at pH 5 and above the permeab-  
ility of the coating to the medicament increases  
and this rise in permeability counteracts the  
reduced solubility of the medicament to reduce the pH  
20 dependence of the release rate. This polymer may  
start to become soluble at pH values lower than 5,  
for example at 3.5 or 4. The preferred polymer for  
this purpose is hydroxypropylmethylcellulose phthalate.  
Other polymers which are suitable for this purpose  
25 include copolymers of the lower alkyl methacrylates  
and polyvinylacetate phthalate.
- The third polymer used should be one which is  
insoluble at all pH values normally encountered in  
the gastrointestinal tract. In the lower gastro-  
30 intestinal tract pH values of about 7.5 are normally  
to be expected and this is the minimum value for



1 insolubility of the third polymer. The preferred  
third polymer is ethyl cellulose. Other polymers  
which may be used include copolymers of the lower  
alkyl methacrylates in which the copolymerising monomer  
5 contains a hydrophilic group.

Other factors which affect the rate of release  
of the medicament present include the thickness of  
the sustaining coating and the ratios of the three  
polymers present in the sustaining coating. Regarding  
10 thickness of the coating the thicker the coating  
the slower the rate of release at all pH values.

The polymer ratios have an important bearing  
upon the rate of release of medicament at all pH  
values. Increase in the ratio of the first polymer  
15 to the third polymer raises the rate of release of  
medicament at low pH values, i.e, in the stomach  
whilst decrease in this ratio reduces the rate of  
release. Increase in the ratio of the second polymer  
to the third polymer increases the rate of release  
20 at pH values above about 5. Increase in the ratio  
of the second polymer to the first polymer without  
changing the proportion of the third polymer increases  
the rate of release at pH values above about 5 and  
decreases the rate of release at pH values below  
25 about 5.

According to a further aspect of the invention  
there is provided a process for producing a pharmaceutical  
composition as defined above wherein the beads are prepared  
by coating inert core particles with particles of the medic-  
30 ament and a binder for adhering said medicament particles  
to said core particles, and applying to said coated core  
particles a sustaining coating solution comprising at least  
the three polymers of differential solubility defined above.

In producing the unit dosage form of the product in accordance  
35 with the invention one may, for example, add 18 parts by weight  
of the three selected polymers to 261 parts by weight of a dispersion  
medium therefor. When the three polymers are cellulose ethers and ether

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1 esters, ethanol is a suitable medium. The resulting  
mixture is stirred until well dispersed and a low  
boiling solvent (e.g. methylene chloride) is then  
added and stirring continued until a clear solution  
5 is obtained. Nonpareils coated with medicaments  
are placed in a coating column or pan and the solution of the three polymers is then gradually fed into  
the column or pan whilst passing a current of warm  
air through the nonpareils until dry coated non-  
10 pareils are obtained.

The dried coated nonpareils are then weighed  
into unit dosage quantities and separate weighed  
quantities are fed into hard gelatine capsules and  
each capsule closed.

15 The following examples illustrate the invention.  
All parts are by weight.

#### PREPARATION 'A'

##### Production of Nonpareils coated with medicament

11 parts hydroxypropylmethylcellulose (Pharmacoat  
20 606) are suspended in 111 parts of purified water  
previously heated to boiling. 440 additional parts  
of water are then added to the suspension and the  
whole stirred until a diluted Pharmacoat suspension  
has formed.

25 11 parts of 1,2-dihydro-6-methyl-2-oxo-5-  
(4-pyridinyl) -nicotinyl nitrile are stirred into  
the Pharmacoat suspension until well dispersed. 200  
parts of nonpareils (sucrose base passing a 25 US  
standard mesh and being retained on a 30 US standard  
30 mesh) are placed in a coating column or pan and  
whilst passing an atomizing current of warm air

- 1 therethrough gradually feed in the diluted Pharmacoat suspension. After all the Pharmacoat suspension has been added continue the passage of the current of warm air until the coated nonpareils are dry.

5 EXAMPLE 1

There are placed in a suitable container 261 parts of ethanol, 11.70 parts of ethyl cellulose, 3.60 parts of hydroxypropylmethylcellulose and 2.70 parts of hydroxypropylmethylcellulose phthalate.

- 10 The solids are stirred in until well dispersed and there is then added to the dispersion 621 parts of methylene chloride. A clear solution should result.

Into a coating column or pan there are placed 222 parts of coated nonpareils prepared as described under Preparation A. Whilst passing an atomising current of warm air through the column the clear solution above described is gradually fed into the coating column or pan. After all the solution has been introduced into the column or pan passage of warm air is continued until the nonpareils are dry.

- 15 The product consisting of nonpareils first coated with medicament and then coated with sustaining coating of three polymers is then removed from the column and after cooling to room temperature, weighed out into portions each containing the required quantity of medicament which are separately fed into standard hard gelatin capsules and closed.

EXAMPLE 2

- 272.72 parts of nonpareils (passing a 25 US standard mesh and being retained on a 30 US standard mesh) were coated with a dispersion prepared from

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- 1 15.0 parts of the same nitrile and 15.0 parts of  
hydroxypropylmethylcellulose (6 centipoises) as  
described in Preparation A.

A sustaining coating solution is prepared from  
5 6 parts of ethylcellulose, 2 parts of hydroxypropyl-  
methylcellulose (6 centipoises) and 2 parts of hydroxy-  
propylmethylcellulose phthalate and used to coat  
the already coated nonpareils as described in Example 1.  
The subsequent procedure is also as described in  
10 Example 1.

#### EXAMPLE 3

Nonpareils are coated with nitrile as described  
in Example 2. A sustaining coating solution is then  
prepared from 12.42 parts of ethylcellulose, 4.14 parts  
15 of hydroxypropylmethylcellulose (6 centipoises) and  
4.14 parts of hydroxypropylmethylcellulose phthalate  
and the subsequent procedure is then as described  
in Example 1.

#### EXAMPLE 4

20 Nonpareils are coated with nitrile as described  
in Example 2. A sustaining coating solution is then  
prepared from 15.95 parts of ethylcellulose, 4.91  
parts of hydroxypropylmethylcellulose and 3.68 parts  
of hydroxypropylmethylcellulose phthalate and the  
25 subsequent procedure is then as described in Example 1.

#### EXAMPLE 5

114 parts of nonpareils (passing a 25 US standard  
mesh and being retained on a 30 US standard mesh) were  
coated with a dispersion prepared from 15 parts of the  
30 same nitrile and 6.0 parts of hydroxypropylmethyl-  
cellulose (6 centipoises) as described in

- 1 Preparation A. A sustaining coating solution is  
prepared from 5.63 parts of ethylcellulose, 1.88  
parts of hydroxypropylmethylcellulose (6 centipoises)  
and 1.88 parts of hydroxypropylmethylcellulose phthalate  
5 and used to coat the already coated nonpareils as  
described in Example 1. The subsequent procedure  
is also as described in Example 1.

EXAMPLE 6

- Nonpareils are coated with nitrile as described  
10 in Example 5. A sustaining coating solution is then  
prepared from 6.0 parts of ethylcellulose, 1.90 parts  
of hydroxypropylmethylcellulose (6 centipoises) and  
2.10 parts of hydroxypropylmethylcellulose phthalate.  
The subsequent procedure is then as described in  
15 Example 1.

- Other nitriles having the general formula I  
have been prepared in sustained form by proceeding  
in the same manner as that illustrated in the above  
examples and the method is applicable to other solid  
20 medicaments having an elimination half-life of the  
order of 0.5 to 4 hours that can be applied to a core  
such as a nonpareil. In addition to cores formed  
of one or more normally crystalline sugars, with or  
without cellulose, inorganic materials such as calcium  
25 phosphate may be used as the core material.

- The availability of sustained release formulations  
in accordance with this invention is of great assistance  
to the patient since it means that a patient does  
not need a unit dosage as frequently as would otherwise  
30 be the case to maintain effective blood levels of

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1 medicament. This minimises the risk of omission to  
take a dose at the correct time as well as avoiding  
the need to take a dose during the night.

The action of the controlled in vivo release  
5 resulting from the use of the formulations in acc-  
ordance with the invention results in controlled and  
reproducible therapy by avoiding peak and trough  
periods in the plasma levels of patients taking the  
prescribed medicament. Such peaks and troughs are  
10 otherwise readily observable with a medicament having  
as short an elimination half-life period as 1 or 3  
hours. A continuous release of medicament during  
passage through the stomach and the gastrointestinal  
tract is secured by the use of three polymers as  
15 described and this is effected in a simple coating  
operation.

The products of the present invention have been  
compared with conventional caplets containing an  
equal total weight of 1.12-dihydro-6-methyl-2-oxo-  
20 5-(4 pyridinyl-nicotinylitrile) (Compound A) in order  
to determine the bioavailability of the compound when  
administered to a patient in those forms. The products  
of the present invention were made up using nonpareils  
as the core material so that each capsule contained

25	Compound A	15. 0 mg
	Pharmacoat 606	6. 0 mg
	Nonpareils (25-30 mesh)	114. 0 mg
	Ethyl cellulose	6. 00 mg
	Pharmacoat 606	1. 90 mg
30	HP-50 (hydroxypropylmethyl cellulose)	2. 10 mg

- 1 The total weight of the filling for each capsule shell was 145.0 mg and this contained 15.0 mg of Compound A.

- 5 The conventionally formulated caplets respectively contained 5 mg and 10 mg of Compound A, one of each being administered to provide the reference quantity of Compound A. The compositions of the two caplets were as follows:

## Core:

10	Compound A	10 mg	5 mg
	Lactose Excipient	209 mg	104.5 mg
	Pre-gelatinized starch	80 mg	40 mg
15	Microcrystalline cellulose AVICEL	100 mg	50 mg
	Magnesium stearate	<u>1 mg</u>	<u>0.5 mg</u>
	Core total:	400 mg	200 mg

## Coating:

20	Hydroxypropyl-methylcellulose	8.33 mg	3.7 mg
	Glyceryl triacetate	1.67 mg	0.739 mg
	Titanium Dioxide	0.265 mg	1.480 mg
	Quinolone Yellow Lake	0.175 mg	0.0704 mg
25	Erythrosine Lake	0.060 mg	
	Indigo Carmine Lake		<u>0.0131 mg</u>
	Total	410.5 mg	206.0 mg

- 30 The conventional caplets and capsules were given to a number of volunteers and the concentrations of Compound A in the plasma of the volunteers at various time intervals from 0.17 to 24 hours from the time of administration were determined. Graphs were prepared

1 from the results obtained. An interval of one week  
was allowed between the first and second treatments  
for each volunteer.

Samples of plasma were taken from each volunteer  
5 at 10, 20, 30 and 45 minutes during the first hour  
after administration, then at half hourly intervals  
for 1 to 4 hours and then at 5, 6, 8, 11, 14 and 24  
hours after administration. Parameters determined  
included maximum drug concentration in the plasma  
10 ( $C_{max}$ ), time to reach maximum concentration ( $t_{max}$ ).  
From the graphs drawn up the area under the curves  
of plasma concentration against time up to the last  
point of sampling was calculated using the trapezoidal  
rule (AUC). The graphs provided plasma profiles  
15 for the several test formulations from which the  
following mean data were read:

	<u><math>C_{max}</math> ng/ml</u>	<u><math>T_{max}</math> Time (hrs)</u>
Conventional caplets	422	0.67
Capsules	138	2.95

20 The plasma profiles with capsules were much flatter  
and broader than those obtained with caplets.

The mean relative bioavailability was 92%.  
This figure is based upon the areas AUC under the  
graph determined as outlined above.

25 The number of volunteers for whom the bio-  
availability was at least 75% of that obtained from  
caplets was 10 out of 10 in the case of capsules.  
The 75% figure is regarded as a criterion for a  
satisfactory sustained release formulation and it  
30 is apparent that this is consistently obtained in

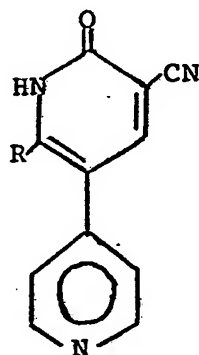


- 1 the case of the capsules. No adverse reactions were reported by volunteers to whom a capsule had been given. It thus becomes apparent that capsules are a very satisfactory way of formulating materials having
- 5 high solubility in gastric juices and lower, but nevertheless appreciable, solubility in the juices present in the small intestine to obtain a sustained release form.

CLAIMS

- 1 1. A pharmaceutical composition of a medicament in  
sustained release unit dosage form for oral adminis-  
tration, comprising a plurality of beads within a  
closed container of a gastric juice-soluble material,  
5 characterized in that each said bead has an inert  
particulate core having adhered thereto a coating  
of particles of said medicament, said coating of  
medicament being surrounded by a sustaining coating  
comprising at least three admixed polymers, a first  
10 said polymer being soluble in gastric juices at all  
pH values encountered in the gastrointestinal tract,  
a second said polymer being substantially insoluble  
in gastric juices at pH values below 3 but soluble  
therein at pH values of 5 and above and the third  
15 said polymer being insoluble in the contents of  
the gastrointestinal tract at all pH values normally  
encountered therein, and the three polymers being  
present in such proportions as to permit a substantially  
uniform release of the medicament during passage  
20 of the beads through the stomach and gastrointestinal  
tract.
2. A pharmaceutical composition according to claim  
1, characterized in that the weight of the insoluble  
third polymer in the sustaining coating is greater  
25 than the sum of the weights of the other two said  
polymers.
3. A pharmaceutical composition according to claim  
2, characterized in that the ratio of the weight  
of the third polymer to the sum of the weights of  
30 the other two polymers is from 3:2 to 2:1.

4. A pharmaceutical composition according to any preceding claim, characterized in that said first polymer constitutes 20 wt.% or less of the polymer mixture forming the sustaining coating.
5. A pharmaceutical composition according to any preceding claim, characterized in that the medicament is a pyridyl-(1H)-pyridone having the general formula:



(I)

- wherein R is an alkyl group having 1 to 4 carbon atoms, or a solid derivative thereof.
- 10 6. A pharmaceutical composition according to any preceding claim, characterized in that the inert cores of the beads are in the form of nonpareils.
7. A pharmaceutical composition according to any preceding claim, characterized in that said first
- 15 polymer is selected from hydroxypropylmethylcellulose and polyvinylpyrrolidone.
8. A pharmaceutical composition according to any preceding claim, characterized in that said second polymer is hydroxypropylmethylcellulose phthalate.
- 20 9. A pharmaceutical composition according to any preceding claim, characterized in that said third polymer is ethyl cellulose.

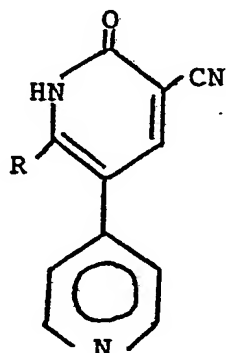
1 10. A process for producing a pharmaceutical  
composition of a medicament in sustained release  
unit dosage form for oral administration, comprising  
a plurality of beads within a closed container of  
5 a gastric juice-soluble material, characterized in  
that said beads are prepared by:

coating inert core particles with particles  
of said medicament and a binder for adhering said  
medicament particles to said core particles and  
10 applying to said coated core particles a  
sustaining coating solution comprising at least three  
admixed polymers, a first said polymer being soluble  
in gastric juices at all pH values encountered in the  
gastrointestinal tract, a second said polymer being  
15 substantially insoluble in gastric juices at pH  
values below 3 but soluble therein at pH values of  
5 and above and the third said polymer being insoluble  
in the contents of the gastrointestinal tract at all  
pH values normally encountered therein, and the three  
20 polymers being present in such proportions as to  
permit a substantially uniform release of the medic-  
ament during passage of the beads through the stomach  
and gastrointestinal tract.

11. A process according to claim 10, characterized  
25 in that said sustaining coating is formed by applying  
to the medicament-coated core particles a solution  
of said three polymers in a volatile solvent therefor  
and evaporating the solvent from the particles thus  
coated.

30 12. A process according to claim 11, characterized  
in that said solution is produced by forming a disper-  
sion of the three polymers in a suitable medium,  
adding a low boiling solvent to the dispersion and  
stirring to give a clear solution.

13. A process according to claim 11 or claim 12, characterized in that the sustaining coating is applied by placing the medicament-coated core particles in a coating column or pan and feeding the polymer solution into the column or pan while passing a current of air through the particles to produce dry coated beads.
14. A process according to any one of claims 10 to 13, characterized in that the medicament is a pyridyl-(1H)-pyridone having the general formula:



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wherein R is an alkyl group having 1 to 4 carbon atoms, or a solid derivative thereof.

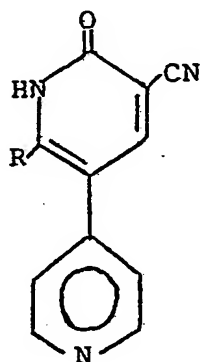
CLAIMS

- 1 1. A process for producing a pharmaceutical composition of a medicament in sustained release unit dosage form for oral administration, comprising a plurality of beads within a closed container of a gastric juice-soluble material, characterised in that said beads are prepared by:
- coating inert core particles with particles of said medicament and a binder for adhering said medicament particles to said core particles and
- 10 applying to said coated core particles a sustaining coating solution comprising at least three admixed polymers, a first said polymer being soluble in gastric juices at all pH values encountered in the gastrointestinal tract, a second said polymer
- 15 being substantially insoluble in gastric juices at pH values below 3 but soluble therein at pH values of 5 and above and the third said polymer being insoluble in the contents of the gastrointestinal tract at all pH values normally encountered therein,
- 20 and the three polymers being present in such proportions as to permit a substantially uniform release of the medicament during passage of the beads through the stomach and gastrointestinal tract.
2. A process according to claim 1, characterised
- 25 in that said sustaining coating is formed by applying to the medicament-coated core particles a solution of said three polymers in a volatile solvent therefor and evaporating the solvent from the particles thus coated.
- 30 3. A process according to claim 2, characterised in that said solution is produced by forming a disper-

1 sion of the three polymers in a suitable medium,  
adding a low boiling solvent to the dispersion and  
stirring to give a clear solution.

4. A process according to claim 2 or claim 3,  
5 characterised in that the sustaining coating is applied  
by placing the medicament-coated core particles in  
a coating column or pan and feeding the polymer solution  
into the column or pan while passing a current of  
air through the particles to produce dry coated beads.

10 5. A process according to any preceding claim  
characterised in that the medicament is a pyridyl-  
(1H)-pyridone having the general formula:



(I)

15 wherein R is an alkyl group having 1 to 4 carbon atoms,  
or a solid derivative thereof.

25 6. A process according to any  
preceding claim characterised in that the weight  
of the insoluble third polymer in the sustaining  
coating is greater than the sum of the weights of  
the other two said polymers.

30 7. A process according to claim 6,

1 characterised in that the ratio of the weight of  
the third polymer to the sum of the weights of the  
other two polymers is from 3:2 to 2:1.

8. A process according to any  
5 preceding claim, characterised in that said first  
polymer constitutes 20 wt.% or less of the polymer  
mixture forming the sustaining coating.

9. A process according to any  
preceding claim, characterised in that the inert  
10 core particles are in the form of nonpareils.

10. A process according to any  
preceding claim, characterised in that said first  
polymer is selected from hydroxypropylmethylcellulose,  
sodium carboxymethyl cellulose and polyvinylpyrrolidone.

15 11. A process according to any  
preceding claim, characterised in that said second  
polymer is hydroxypropylmethylcellulose phthalate.

12. A process according to any  
preceding claim, characterised in that said third  
20 polymer is ethyl cellulose.